

FROVA- frovatriptan succinate tablet, film coated
Endo Pharmaceuticals Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FROVA® safely and effectively. See full prescribing information for FROVA®.

FROVA® (frovatriptan succinate) tablets, for oral use
Initial U.S. Approval: 2001

----- **RECENT MAJOR CHANGES** -----

Warnings and Precautions (5.6) 11/2012

----- **INDICATIONS AND USAGE** -----

FROVA is a serotonin (5-HT_{1B/1D}) receptor agonist (triptan) indicated for the acute treatment of migraine with or without aura in adults (1)

Limitations of Use

- Use only after a clear diagnosis of migraine has been established (1)
- Not indicated for the prophylactic therapy of migraine (1)
- Not indicated for the treatment of cluster headache (1)

----- **DOSAGE AND ADMINISTRATION** -----

- 1 tablet taken with fluids. Second tablet may be taken 2 hours after initial dose if headache recurs following initial relief. Total dose not to exceed 3 tablets in any 24-hour period (2)

----- **DOSAGE FORMS AND STRENGTHS** -----

Tablets: 2.5 mg (3)

----- **CONTRAINDICATIONS** -----

- History of coronary artery disease or coronary artery vasospasm (4)
- Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders (4)
- History of stroke, transient ischemic attack, or hemiplegic or basilar migraine (4)
- Peripheral vascular disease (4)
- Ischemic bowel disease (4)
- Uncontrolled hypertension (4)
- Recent (within 24 hours) use of treatment with another 5-HT₁ agonist, or an ergotamine-containing medication (4)
- Hypersensitivity to FROVA (angioedema and anaphylaxis seen) (4)

----- **WARNINGS AND PRECAUTIONS** -----

- Myocardial ischemia/infarction or Prinzmetal's angina: Perform cardiac evaluation in patients with multiple cardiovascular risk factors (5.1)
- Arrhythmias: Discontinue FROVA if occurs (5.2)
- Chest/throat/neck/jaw pain, tightness, pressure, or heaviness: Generally not associated with myocardial ischemia; evaluate high risk patients for coronary artery disease (5.3)
- Cerebral hemorrhage, subarachnoid hemorrhage, and stroke: Discontinue FROVA if occurs (5.4)
- Gastrointestinal ischemic reactions and peripheral vasospastic reactions: Discontinue FROVA if occurs (5.5)
- Medication overuse headache: Detoxification may be necessary (5.6)
- Serotonin syndrome: Discontinue FROVA if occurs (5.7, 7.3)

----- **ADVERSE REACTIONS** -----

- Most common adverse reactions (≥2% and >placebo) were dizziness, headache, paresthesia, dry mouth, dyspepsia, fatigue, hot or cold sensation, chest pain, skeletal pain, and flushing (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Endo Pharmaceuticals Inc. at 1-800-462-3636 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----- **USE IN SPECIFIC POPULATIONS** -----

- Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2013

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FROVA is indicated for the acute treatment of migraine with or without aura in adults.

Limitations of Use

- Use only if a clear diagnosis of migraine has been established. If a patient has no response for the first migraine attack treated with FROVA, reconsider the diagnosis of migraine before FROVA is administered to treat any subsequent attacks.
- FROVA is not indicated for the prevention of migraine attacks.
- Safety and effectiveness of FROVA have not been established for cluster headache.

2 DOSAGE AND ADMINISTRATION

Dosing Information

The recommended dose is a single tablet of FROVA (frovatriptan 2.5 mg) taken orally with fluids.

If the migraine recurs after initial relief, a second tablet may be taken, providing there is an interval of at least 2 hours between doses. The total daily dose of FROVA should not exceed 3 tablets (3 x 2.5 mg per 24 hour period).

There is no evidence that a second dose of FROVA is effective in patients who do not respond to a first dose of the drug for the same headache.

The safety of treating an average of more than 4 migraine attacks in a 30-day period has not been established.

3 DOSAGE FORMS AND STRENGTHS

2.5 mg Tablets: Round, white, film-coated tablets debossed with 2.5 on one side and "E" on the other side.

4 CONTRAINDICATIONS

FROVA is contraindicated in patients with:

- Ischemic coronary artery disease (CAD) (e.g. angina pectoris, history of myocardial infarction, or documented silent ischemia), or coronary artery vasospasm, including Prinzmetal's angina [*see Warnings and Precautions (5.1)*].
- Wolff-Parkinson-White Syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders [*see Warnings and Precautions (5.2)*].
- History of stroke, transient ischemic attack (TIA), or history of hemiplegic or basilar migraine because these patients are at a higher risk of stroke [*see Warnings and Precautions (5.4)*].
- Peripheral vascular disease [*see Warnings and Precautions (5.5)*].
- Ischemic bowel disease [*see Warnings and Precautions (5.5)*].
- Uncontrolled hypertension [*see Warnings and Precautions (5.8)*].
- Recent use (i.e., within 24 hours) of another 5-HT₁ agonist, an ergotamine containing or ergot-type medication such as dihydroergotamine (DHE) or methysergide [*see Drug Interactions (7.1, 7.2)*].
- Hypersensitivity to FROVA (angioedema and anaphylaxis seen) [*see Warnings and Precautions (5.9)*].

5 WARNINGS AND PRECAUTIONS

5.1 Myocardial Ischemia, Myocardial Infarction, and Prinzmetal's Angina

FROVA is contraindicated in patients with ischemic or vasospastic CAD. There have been rare reports of serious cardiac adverse reactions, including acute myocardial infarction, occurring within a few hours following administration of FROVA. Some of these reactions occurred in patients without known CAD. FROVA may cause coronary artery vasospasm (Prinzmetal's angina), even in patients without a history of CAD.

Perform a cardiovascular evaluation in triptan-naïve patients who have multiple cardiovascular risk factors (e.g., increased age, diabetes, hypertension, smoking, obesity, strong family history of CAD) prior to receiving FROVA. Do not administer FROVA if there is evidence of CAD or coronary artery vasospasm [see *Contraindications (4)*]. For patients with multiple cardiovascular risk factors who have a negative cardiovascular evaluation, consider administering the first FROVA dose in a medically-supervised setting and performing an electrocardiogram (ECG) immediately following FROVA administration. For such patients, consider periodic cardiovascular evaluation in intermittent long-term users of FROVA.

5.2 Arrhythmias

Life-threatening disturbances of cardiac rhythm including ventricular tachycardia and ventricular fibrillation leading to death have been reported within a few hours following the administration of 5-HT₁ agonists. Discontinue FROVA if these disturbances occur. FROVA is contraindicated in patients with Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders [see *Contraindications (4)*].

5.3 Chest, Throat, Neck, and Jaw Pain/Tightness/Pressure

Sensations of pain, tightness, pressure, and heaviness have been reported in the chest, throat, neck, and jaw after treatment with FROVA and are usually non-cardiac in origin. However, perform a cardiac evaluation if these patients are at high cardiac risk. The use of FROVA is contraindicated in patients with CAD and those with Prinzmetal's angina [see *Contraindications (4)*].

5.4 Cerebrovascular Events

Cerebral hemorrhage, subarachnoid hemorrhage, stroke and other cerebrovascular events have been reported in patients treated with 5-HT₁ agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not.

Before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with symptoms atypical of migraine, other potentially serious neurological conditions need to be excluded. FROVA is contraindicated in patients with a history of stroke or TIA [see *Contraindications (4)*].

5.5 Other Vasospasm Reactions

FROVA, may cause non-coronary vasospastic reactions, such as peripheral vascular ischemia, gastrointestinal vascular ischemia and infarction (presenting with abdominal pain and bloody diarrhea), splenic infarction, and Raynaud's syndrome. In patients who experience symptoms or signs suggestive of a vasospastic reaction following the use of any 5-HT₁ agonist, rule out a vasospastic reaction before using FROVA [see *Contraindications (4)*].

Reports of transient and permanent blindness and significant partial vision loss have been reported with the use of 5-HT₁ agonists. Since visual disorders may be part of a migraine attack, a causal relationship between these events and the use of 5-HT₁ agonists have not been clearly established.

5.6 Medication Overuse Headache

Overuse of acute migraine drugs (e.g., ergotamine, triptans, opioids, or combination of these drugs for 10 or more days per month) may lead to exacerbation of headache (medication overuse headache). Medication overuse headache may present as migraine-like daily headaches or as a marked increase in frequency of migraine attacks. Detoxification of patients, including withdrawal of the overused drugs, and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

5.7 Serotonin Syndrome

Serotonin syndrome may occur with FROVA, particularly during co-administration with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase (MAO) inhibitors [see *Drug Interactions* (7.3)]. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms usually occurs within minutes to hours of receiving a new or a greater dose of a serotonergic medication. Discontinue FROVA if serotonin syndrome is suspected.

5.8 Increase in Blood Pressure

Significant elevation in blood pressure, including hypertensive crisis with acute impairment of organ systems, has been reported on rare occasions in patients treated with 5-HT₁ agonists, including patients without a history of hypertension. Monitor blood pressure in patients treated with FROVA. FROVA is contraindicated in patients with uncontrolled hypertension [see *Contraindications* (4)].

5.9 Anaphylactic/Anaphylactoid Reactions

There have been reports of anaphylaxis, anaphylactoid, and hypersensitivity reactions including angioedema in patients receiving FROVA. Such reactions can be life threatening or fatal. In general, anaphylactic reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens. FROVA is contraindicated in patients with a history of hypersensitivity reaction to FROVA [see *Contraindications* (4)].

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in other sections of the labeling:

- Myocardial ischemia, myocardial infarction, and Prinzmetal's angina [see *Warnings and Precautions* (5.1)]
- Arrhythmias [see *Warnings and Precautions* (5.2)]
- Chest, throat, neck and/or jaw pain/tightness/pressure [see *Warnings and Precautions* (5.3)]
- Cerebrovascular events [see *Warnings and Precautions* (5.4)]
- Other vasospasm reactions [see *Warnings and Precautions* (5.5)]
- Medication overuse headache [see *Warnings and Precautions* (5.6)]
- Serotonin syndrome [see *Warnings and Precautions* (5.7)]
- Increases in blood pressure [see *Warnings and Precautions* (5.8)]
- Hypersensitivity reactions [see *Contraindications* (4) and *Warnings and Precautions* (5.8)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

FROVA was evaluated in four randomized, double-blind, placebo-controlled, short-term trials. These trials involved 2392 patients (1554 on FROVA 2.5 mg and 838 on placebo). In these short-term trials, patients were predominately female (88%) and Caucasian (94%) with a mean age of 42 years (range 18 - 69). The treatment-emergent adverse events that occurred most frequently following administration of FROVA 2.5 mg (*i.e.*, in at least 2% of patients), and at an incidence \geq 1% greater than with placebo, were dizziness, paresthesia, headache, dry mouth, fatigue, flushing, hot or cold sensation, dyspepsia, skeletal pain, and chest pain. In a long term, open-label study where 496 patients were allowed to treat multiple migraine attacks with FROVA 2.5 mg for up to 1 year, 5% of patients (n=26) discontinued due to treatment-emergent adverse events.

Table 1 lists treatment-emergent adverse events reported within 48 hours of drug administration that occurred with FROVA 2.5 mg at an incidence of $\geq 2\%$ and more often than on placebo, in the four placebo-controlled trials. The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these incidence estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ.

Table 1

Treatment-Emergent Adverse Events Reported within 48 Hours (Incidence $\geq 2\%$ and Greater Than Placebo) of Patients in Four Pooled Placebo-Controlled Migraine Trials

Adverse events	FROVA 2.5 mg (n=1554)	Placebo (n=838)
<i>Central & peripheral nervous system</i>		
Dizziness	8%	5%
Headache	4%	3%
Paresthesia	4%	2%
<i>Gastrointestinal system disorders</i>		
Dry mouth	3%	1%
Dyspepsia	2%	1%
<i>Body as a whole – general disorders</i>		
Fatigue	5%	2%
Hot or cold sensation	3%	2%
Chest pain	2%	1%
<i>Musculo-skeletal</i>		
Skeletal pain	3%	2%
<i>Vascular</i>		
Flushing	4%	2%

The incidence of adverse events in clinical trials did not increase when up to 3 doses were used within 24 hours. The incidence of adverse events in placebo-controlled clinical trials was not affected by gender, age or concomitant medications commonly used by migraine patients. There were insufficient data to assess the impact of race on the incidence of adverse events.

Other Events Observed in Association with the Administration of FROVA

The incidence of frequently reported adverse events in four placebo-controlled trials are presented below. Events are further classified within body system categories. Frequent adverse events are those occurring in at least 1/100 patients.

Central and peripheral nervous system: dysesthesia and hypoesthesia.

Gastrointestinal: vomiting, abdominal pain and diarrhea.

Body as a whole: pain.

Psychiatric: insomnia and anxiety.

Respiratory: sinusitis and rhinitis.

Vision disorders: vision abnormal.

Skin and appendages: sweating increased.

Hearing and vestibular disorders: tinnitus.

Heart rate and rhythm: palpitation.

6.2 Postmarketing Experience

The following adverse reactions were identified during post approval use of FROVA. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Central and peripheral nervous system: Seizure.

7 DRUG INTERACTIONS

7.1 Ergot-containing Drugs

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and FROVA within 24 hours of each other is contraindicated [see *Contraindications* (4)].

7.2 5-HT_{1B/1D} Agonists

Because their vasospastic effects may be additive, co-administration of FROVA and other 5-HT₁ agonists (e.g., triptans) within 24 hours of each other is contraindicated [see *Contraindications* (4)].

7.3 Selective Serotonin Reuptake Inhibitors / Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome

Cases of serotonin syndrome have been reported during combined use of triptans and SSRIs, SNRIs, TCAs, and MAO inhibitors [see *Warnings and Precautions* (5.7)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled trials in pregnant women; therefore, frovatriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When pregnant rats were administered frovatriptan during the period of organogenesis at oral doses of 100, 500 and 1000 mg/kg/day (equivalent to 130, 650 and 1300 times the maximum recommended human dose [MRHD] of 7.5 mg/day on a mg/m² basis) there were dose related increases in incidences of fetuses with dilated ureters, unilateral and bilateral pelvic cavitation, hydronephrosis, and hydroureters. A no-effect dose for renal effects was not established. This signifies a syndrome of related effects on a specific organ in the developing embryo in all treated groups, which is consistent with a slight delay in fetal maturation. This delay was also indicated by a treatment related increased incidence of incomplete ossification of the sternebrae, skull and nasal bones in all treated groups. Reduced fetal weights and an increased incidence of embryoletality were observed in treated rats; an increase in embryoletality occurred in both the embryo-fetal developmental study and in the prenatal-postnatal developmental study. No increase in embryoletality was observed at the lowest dose level studied (100 mg/kg/day, equivalent to 130 times the MRHD on a mg/m² basis). When pregnant rabbits were dosed throughout organogenesis at oral doses up to 80 mg/kg/day (equivalent to 210 times the MRHD on a mg/m² basis), no effects on fetal development were observed.

8.3 Nursing mothers

It is not known whether frovatriptan is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from FROVA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

In rats, oral dosing with frovatriptan resulted in levels of frovatriptan and/or its metabolites in milk up to four times higher than in plasma.

8.4 Pediatric use

The safety and effectiveness in pediatric patients have not been established. Therefore, FROVA is not recommended for use in patients under 18 years of age. There are no additional adverse reactions identified in pediatric patients based on postmarketing experience that were not previously identified in adults.

8.5 Geriatric use

Mean blood concentrations of frovatriptan in elderly patients were 1.5- to 2-times higher than those seen in younger adults [see *Clinical Pharmacology* (12.3)]. No dosage adjustment is necessary.

8.6 Patients with Hepatic Impairment

No dosage adjustment is necessary when FROVA is given to patients with mild to moderate hepatic impairment.

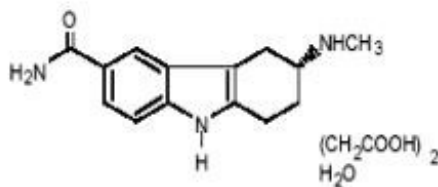
There is no clinical or pharmacokinetic experience with FROVA in patients with severe hepatic impairment. Because a greater than two-fold increase in AUC is predicted in patients with severe hepatic impairment, there is a greater potential for adverse events in these patients, and FROVA should therefore be used with caution in that population.

10 OVERDOSAGE

The elimination half-life of frovatriptan is 26 hours [see *Clinical Pharmacology* (12.3)]. Therefore, monitoring of patients after overdose with frovatriptan should continue for at least 48 hours or while symptoms or signs persist. There is no specific antidote to frovatriptan. It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentrations of frovatriptan.

11 DESCRIPTION

FROVA (frovatriptan succinate) tablets contain frovatriptan succinate, a selective 5-hydroxy-tryptamine₁ (5-HT_{1B/1D}) receptor subtype agonist (triptan), as the active ingredient. Frovatriptan succinate is chemically designated as R-(+) 3-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole monosuccinate monohydrate and it has the following structure:



The empirical formula is C₁₄H₁₇N₃O₄·C₄H₆O₄·H₂O, representing a molecular weight of 379.4. Frovatriptan succinate is a white to off-white powder that is soluble in water.

Each FROVA tablet for oral administration contains 3.91 mg frovatriptan succinate, equivalent to 2.5 mg of frovatriptan base. Each tablet also contains the inactive ingredients lactose NF, microcrystalline cellulose NF, colloidal silicon dioxide NF, sodium starch glycolate NF, magnesium stearate NF, hypromellose USP, polyethylene glycol 3000 USP, triacetin USP, and titanium dioxide USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Frovatriptan binds with high affinity to 5-HT_{1B/1D} receptors. The therapeutic activity of FROVA is thought to be due to the agonist effects at the 5-HT_{1B/1D} receptors on intracranial blood vessels (including the arterio-venous anastomoses) and sensory nerves of the trigeminal system which result in cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release.

12.3 Pharmacokinetics

The pharmacokinetics of frovatriptan are similar in migraine patients and healthy subjects.

Absorption

Mean maximum blood concentrations (C_{max}) in patients are achieved approximately 2 - 4 hours after administration of a single oral dose of frovatriptan 2.5 mg. The absolute bioavailability of an oral dose of frovatriptan 2.5 mg in healthy subjects is about 20% in males and 30% in females. Food has no significant effect on the bioavailability of frovatriptan, but delays t_{max} by one hour.

Distribution

Binding of frovatriptan to serum proteins is low (approximately 15%). Reversible binding to blood cells at equilibrium is approximately 60%, resulting in a blood: plasma ratio of about 2:1 in both males and females. The mean steady state volume of distribution of frovatriptan following intravenous administration of 0.8 mg is 4.2 L/kg in males and 3.0 L/kg in females.

Metabolism

In vitro, cytochrome P450 1A2 appears to be the principal enzyme involved in the metabolism of frovatriptan. Following administration of a single oral dose of radiolabeled frovatriptan 2.5 mg to healthy male and female subjects, 32% of the dose was recovered in urine and 62% in feces. Radiolabeled compounds excreted in urine were unchanged frovatriptan, hydroxylated frovatriptan, N-acetyl desmethyl frovatriptan, hydroxylated N-acetyl desmethyl frovatriptan and desmethyl frovatriptan, together with several other minor metabolites. Desmethyl frovatriptan has lower affinity for 5-HT_{1B/1D} receptors compared to the parent compound. The N-acetyl desmethyl metabolite has no significant affinity for 5-HT receptors. The activity of the other metabolites is unknown.

Elimination

After an intravenous dose, mean clearance of frovatriptan was 220 and 130 mL/min in males and females, respectively. Renal clearance accounted for about 40% (82 mL/min) and 45% (60 mL/min) of total clearance in males and females, respectively. The mean terminal elimination half-life of frovatriptan in both males and females is approximately 26 hours.

Special Populations

Hepatic Impairment

The AUC of frovatriptan in patients with mild (Child-Pugh 5-6) to moderate (Child-Pugh 7-9) hepatic impairment was about twice that of young, healthy subjects, but within the range observed in healthy elderly subjects and was considerably lower than the values attained with higher doses of frovatriptan (up to 40 mg), which were not associated with any serious adverse effects. There is no clinical or pharmacokinetic experience with FROVA in patients with severe hepatic impairment.

Renal Impairment

The pharmacokinetics of frovatriptan following a single oral dose of 2.5 mg was not different in patients with renal impairment (5 males and 6 females, creatinine clearance 16 - 73 mL/min) compared to subjects with normal renal function.

Age

Mean AUC of frovatriptan was 1.5- to 2-fold higher in healthy elderly subjects (age 65 – 77 years)

compared to those in healthy younger subjects (age 21 - 37 years). There was no difference in t_{\max} or $t_{1/2}$ between the two populations.

Sex

There was no difference in the mean terminal elimination half-life of frovatriptan in males and females. Bioavailability was higher, and systemic exposure to frovatriptan was approximately 2-fold greater, in females than males, irrespective of age.

Race

The effect of race on the pharmacokinetics of frovatriptan has not been examined.

Drug Interaction Studies

Frovatriptan is not an inhibitor of human monoamine oxidase (MAO) enzymes or cytochrome P450 (isozymes 1A2, 2C9, 2C19, 2D6, 2E1, 3A4) *in vitro* at concentrations up to 250 to 500- fold higher than the highest blood concentrations observed in man at a dose of 2.5 mg. No induction of drug metabolizing enzymes was observed following multiple dosing of frovatriptan to rats or on addition to human hepatocytes *in vitro*. Although no clinical trials have been performed, it is unlikely that frovatriptan will affect the metabolism of co-administered drugs metabolized by these mechanisms.

Oral Contraceptives

Retrospective analysis of pharmacokinetic data from females across trials indicated that the mean C_{\max} and AUC of frovatriptan are 30% higher in those subjects taking oral contraceptives compared to those not taking oral contraceptives.

Ergotamine

The AUC and C_{\max} of frovatriptan (2 x 2.5 mg dose) were reduced by approximately 25% when co-administered with ergotamine tartrate [see *Contraindications (4)*, *Drug Interactions (7.1)*].

Propranolol

Propranolol increased the AUC of frovatriptan 2.5 mg in males by 60% and in females by 29%. The C_{\max} of frovatriptan was increased 23% in males and 16% in females in the presence of propranolol. The t_{\max} as well as half-life of frovatriptan, though slightly longer in the females, were not affected by concomitant administration of propranolol.

Moclobemide

The pharmacokinetic profile of frovatriptan was unaffected when a single oral dose of frovatriptan 2.5 mg was administered to healthy female subjects receiving the MAO-A inhibitor, moclobemide, at an oral dose of 150 mg bid for 8 days.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of orally administered frovatriptan was evaluated in an 84-week study in mice (4, 13, and 40 mg/kg/day), a 104-week study in rats (8.5, 27 and 85 mg/kg/day), and a 26-week study in p53(+/-) transgenic mice (20, 62.5, 200, and 400 mg/kg/day). Although a maximum tolerated dose was not achieved in the 84-week mouse study and in female rats, plasma exposures at the highest doses studied were higher than that achieved in humans at the maximum recommended human dose (MRHD) of 7.5 mg/day. There were no increases in tumor incidence in the 84-week mouse study at doses producing plasma exposures (AUC) 140 times that in humans at the MRHD. In the rat study, there was a statistically significant increase in the incidence of pituitary adenomas in males only at 85 mg/kg/day, a dose associated with a plasma AUC 250 times that in humans at the MRHD. In the 26-week p53(+/-)

transgenic mouse study, the incidence of subcutaneous sarcomas was increased in females at doses of 200 and 400 mg/kg/day.

These sarcomas were associated with subcutaneously implanted animal identification transponders, and are not considered to be relevant to humans. There were no other increases in tumor incidence of any type in any dose group.

Mutagenesis

Frovatriptan was clastogenic in human lymphocyte cultures, in the absence of metabolic activation. In the bacterial reverse mutation assay (Ames test), frovatriptan produced an equivocal response in the absence of metabolic activation. Frovatriptan was negative in an *in vitro* mouse lymphoma *tk* assay and an *in vivo* mouse bone marrow micronucleus test.

Impairment of Fertility

Male and female rats were dosed orally with frovatriptan prior to and during mating and in females up to implantation, at doses of 100, 500, and 1000 mg/kg/day (equivalent to approximately 130, 650, and 1300 times the MRHD on a mg/m² basis). At all dose levels, there was an increase in the number of females that mated on the first day of pairing compared to control animals. This occurred in conjunction with a prolongation of the estrous cycle. In addition, females had a decreased mean number of corpora lutea, and consequently a lower number of live fetuses per litter, which suggested a partial impairment of ovulation. There were no other fertility-related effects.

14 CLINICAL STUDIES

The efficacy of FROVA in the acute treatment of migraine headaches was demonstrated in four randomized, double-blind, placebo-controlled, short-term outpatient trials. In these trials, patients received doses of frovatriptan from 0.5 mg to 40 mg. In these controlled short-term trials, patients were predominately female (88%) and Caucasian (94%) with a mean age of 42 years (range 18 - 69). Patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction in headache severity from moderate or severe pain to mild or no pain, was assessed for up to 24 hours after dosing. The associated symptoms nausea, vomiting, photophobia and phonophobia were also assessed. Maintenance of response was assessed for up to 24 hours post dose. In two of the trials a second dose of FROVA was provided after the initial treatment, to treat recurrence of the headache within 24 hours. Other medication, excluding other 5-HT₁ agonists and ergotamine containing compounds, was permitted from 2 hours after the first dose of FROVA. The frequency and time to use of additional medications were also recorded.

In all four placebo-controlled trials, the percentage of patients achieving a headache response 2 hours after treatment was significantly greater for those taking FROVA 2.5 mg compared to those taking placebo (Table 2).

Lower doses of frovatriptan (1 mg or 0.5 mg) were not effective at 2 hours. Higher doses (5 mg to 40 mg) of frovatriptan showed no added benefit over 2.5 mg but did cause a greater incidence of adverse events.

Table 2

Percentage of Patients with Headache Response (Mild or No Headache) 2 Hours Following Treatment^a

Trial	FROVA 2.5 mg	Placebo
1	42%* (n=90)	22% (n=91)
2	39%* (n=187)	21% (n=99)
3	46%** (n=672)	27% (n=347)
4	37%** (n=438)	23% (n=225)

^a ITT observed data, excludes patients who had missing data or were asleep; * $p < 0.05$, ** $p < 0.001$ in comparison with placebo

The estimated probability of achieving an initial headache response by 2 hours following treatment is depicted in Figure 1.

Figure 1

Estimated Probability of Achieving Initial Headache Response Within 2 Hours

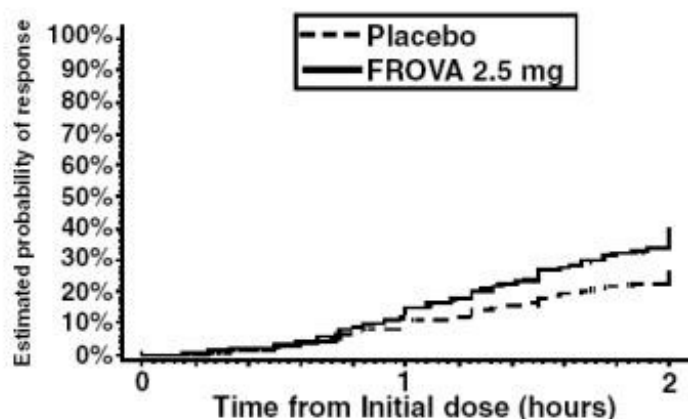


Figure 1 shows a Kaplan-Meier plot of the probability over time of obtaining headache response (no or mild pain) following treatment with FROVA 2.5 mg or placebo. The probabilities displayed are based on pooled data from the four placebo-controlled trials described in Table 2. Patients who did not achieve a response were censored at 24 hours.

In patients with migraine-associated nausea, photophobia and phonophobia at baseline there was a decreased incidence of these symptoms in FROVA treated patients compared to placebo.

The estimated probability of patients taking a second dose or other medication for their migraine over the 24 hours following the initial dose of study treatment is summarized in Figure 2.

Figure 2

Estimated Probability of Patients Taking a Second Dose or Other Medication for Migraine Over the 24 Hours Following the Initial Dose of Study Treatment

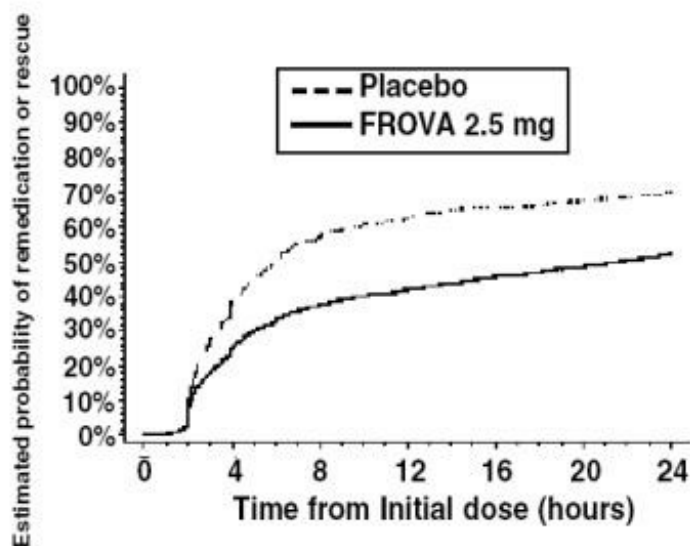


Figure 2 is a Kaplan-Meier plot showing the probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study medication based on the data from the four placebo-controlled trials described in Table 2. The plot includes those patients who had a response to the initial dose and those who did not. The protocols did not permit remedication within 2 hours of the initial dose.

Efficacy was unaffected by a history of aura; gender; age, or concomitant medications commonly used by migraine patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

FROVA tablets, containing 2.5 mg of frovatriptan (base) as the succinate salt, are available as round, white, film-coated tablets debossed with 2.5 on one side and “E” on the other side. The tablets are available in:

Blister card of 9 tablets, 1 blister card per carton (NDC 63481-025-09)

Store FROVA tablets at controlled room temperature, 25°C (77°F) excursions permitted to 15 - 30°C (59°F - 86°F) [see USP Controlled Room Temperature]. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information)

Myocardial Ischemia and/or Infarction, Prinzmetal’s Angina, Other Vasospastic Reactions, and Cerebrovascular Events

Inform patients that FROVA may cause serious cardiovascular adverse reactions such as myocardial infarction or stroke, which may result in hospitalization and even death. Although serious cardiovascular reactions can occur without warning symptoms, instruct patients to be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and instruct them to ask for medical advice when observing any indicative sign or symptoms. Instruct patients to seek medical advice if they have symptoms of other vasospastic reactions [see Warnings and Precautions (5.1, 5.2, 5.4, 5.5, and 5.8)].

Anaphylactic/Anaphylactoid Reactions

Inform patients that anaphylactic/anaphylactoid reactions have occurred in patients receiving FROVA. Such reactions can be life threatening or fatal. In general, anaphylactic reactions to drugs are more

likely to occur in individuals with a history of sensitivity to multiple allergens [see *Contraindications (4)*].

Medication Overuse Headache

Inform patients that use of drugs to treat acute migraines for 10 or more days per month may lead to an exacerbation of headache, and encourage patients to record headache frequency and drug use (e.g., by keeping a headache diary) [see *Warnings and Precautions (5.6)*].

Serotonin Syndrome

Inform patients about the risk of serotonin syndrome with the use of FROVA or other triptans, particularly during combined use with SSRIs, SNRIs, TCAs, and MAO inhibitors [see *Warnings and Precautions (5.7)* and *Drug Interactions (7.3)*].

Pregnancy

Inform patients that FROVA should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus [see *Use in Specific Populations (8.1)*].

Nursing Mothers

Inform patients to notify their healthcare provider if they are breastfeeding or plan to breastfeed [see *Use in Specific Populations (8.3)*].

PATIENT LABELING

Patient Information

FROVA[®] (FRO-va) (frovatriptan succinate)

Tablets

Read this Patient Information before you start taking FROVA and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor. You and your doctor should discuss FROVA when you start taking your medication and at regular check-ups.

What is FROVA?

FROVA is a prescription medicine used to treat migraine headaches with or without aura in adults.

FROVA is not used to treat other types of headaches.

FROVA is not used to prevent or decrease the number of migraine headaches.

It is not known if FROVA is safe and effective to treat cluster headaches.

It is not known if FROVA is safe and effective in children under 18 years of age.

Who should not take FROVA?

Do not take FROVA if you have:

- heart problems, a history of heart problems, or problems with the electrical system of your heart
- had a stroke, transient ischemic attacks (TIAs), or problems with your blood circulation
- hemiplegic migraines or basilar migraines. If you are not sure if you have these types of migraines, ask your healthcare provider.
- narrowing of blood vessels to your legs, arms, or stomach (peripheral vascular disease)
- uncontrolled high blood pressure
- taken any of the following medicines in the last 24 hours:
 - almotriptan (AXERT[®])
 - eletriptan (RELPAX[®])
 - naratriptan (AMERGE[®])
 - rizatriptan (MAXALT[®], MAXALT-MLT[®])

- sumatriptan (IMITREX[®], SUMAVEL[®] DosePro[®], ALSUMA[®])
 - sumatriptan and naproxen (TREXIMET[®])
 - zolmitriptan (ZOMIG[®])
 - Ergotamine or ergotamine-type medicines (BELLERGAL[®], CAFERGOT[®], ERGOMAR[®], WIGRAINE[®], D.H.E.45[®], MIGRANAL[®], SANSERT[®])
- Ask your healthcare provider if you are not sure if your medicine is listed above.
- an allergy to frovatriptan or any of the ingredients in FROVA. See the end of this leaflet for a complete list of ingredients in FROVA.

What should I tell my doctor before taking FROVA?

Before you take FROVA, tell your doctor about all of your medical conditions, including if you:

- have high blood pressure
- have high cholesterol
- have diabetes
- smoke
- are overweight
- are a female who has gone through menopause
- have heart disease or a family history of heart disease or stroke
- are pregnant or plan to become pregnant
- are breastfeeding or plan to breastfeed

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

Especially tell your doctor if you take:

- propranolol
- selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), two types of drugs for depression or other disorders. Common SSRIs are CELEXA[®] (citalopram HBr), LEXAPRO[®] (escitalopram oxalate), PAXIL[®] (paroxetine), PROZAC[®]/SARAFEM[®] (fluoxetine), SYMBAX[®] (olanzapine/fluoxetine), ZOLOFT[®] (sertraline), and fluvoxamine. Common SNRIs are CYMBALTA[®] (duloxetine) and EFFEXOR[®] (venlafaxine).

These medicines may affect how FROVA works, or FROVA may affect how these medicines work.

Ask your doctor or pharmacist for a list of these medicines if you are not sure.

Know the medicines you take. Keep a list of them to show your doctor or pharmacist when you get a new medicine.

How should I take FROVA?

- Certain people should take their first dose of FROVA in their doctor's office or in another medical setting. Ask your doctor if you should take your first dose in a medical setting.
- Take FROVA exactly as your doctor tells you.
- If you do not get any relief after your first FROVA tablet, do not take a second tablet without first talking with your doctor.
- If your headache comes back or you only get some relief from your headache, you may take a second FROVA tablet 2 hours after the first tablet.
- Do not take more than 3 FROVA tablets in a 24-hour period.
- It is not known if it is safe and effective to take FROVA for more than 4 headaches in 30 days.
- If you take too much FROVA, call your doctor or go to the nearest hospital emergency room right away.
- You should write down when you have headaches and when you take FROVA so you can talk with your doctor about how FROVA is working for you.

What should I avoid while taking FROVA?

FROVA can cause dizziness, weakness, or drowsiness. If you have these symptoms do not drive a car, use machinery, or do anything where you need to be alert.

What are the possible side effects of FROVA?

FROVA can cause serious side effects.

Call your doctor right away if you have any of the following symptoms after taking FROVA:

- **Heart attack or other heart problems.** Heart problems may lead to death. Stop taking FROVA and get emergency medical help right away if you have any of the following symptoms of a heart attack or other heart problems:
 - Discomfort in the center of your chest that lasts for more than a few minutes, or that goes away and comes back
 - Chest pain or chest discomfort that feels like heavy pressure, squeezing, or fullness
 - Pain or discomfort in your arms, back, neck, jaw, or stomach
 - Shortness of breath with or without chest discomfort
 - Breaking out in a cold sweat
 - Feeling lightheaded
 - Nausea or vomiting with any of the symptoms included above
- **Stroke.** Symptoms of stroke include face drooping, slurred speech, and unusual weakness or numbness.
- **Changes in color or sensation in your fingers and toes (Raynaud's syndrome).**
- **Stomach and intestinal problems** (gastrointestinal and colonic ischemic events). Symptoms of gastrointestinal and colonic ischemic events include:
 - Sudden or severe stomach pain
 - Stomach pain after meals
 - Weight loss
 - Nausea or vomiting
 - Constipation or diarrhea
 - Bloody diarrhea
 - Fever
- **Problems with blood circulation to your legs and feet** (peripheral vascular ischemia). Symptoms of peripheral vascular ischemia include:
 - Cramping and pain in your legs or hips
 - Feeling of heaviness or tightness in your leg muscles
 - Burning or aching pain in your feet or toes while resting
 - Numbness, tingling, or weakness in your legs
 - Cold feeling or color changes in one or both legs or feet
- **Increased blood pressure**
- **Allergic reactions.** Symptoms of allergic reaction include:
 - Rash
 - Hives
 - Itching
 - Swelling of the face, mouth, throat, or tongue
 - Difficulty breathing
- **Medication overuse headache.** Some people who use too many FROVA tablets may have worse headaches (medication overuse headache). If your headaches get worse, your doctor may decide to stop your treatment with FROVA.
- **Serotonin syndrome.** Serotonin syndrome is a rare but serious problem that can happen in people using FROVA, especially if FROVA is used with anti-depressant medicines called SSRIs and SNRIs. Call your doctor right away if you have any of the following symptoms of serotonin

syndrome:

- Mental changes such as seeing things that are not there (hallucinations), agitation, or coma
- Fast heartbeat
- Changes in blood pressure
- High body temperature
- Tight muscles
- Trouble walking

The most common side effects of FROVA are:

- dizziness
- fatigue (tiredness)
- headache (other than a migraine headache)
- paresthesia (feeling of tingling)
- dry mouth
- flushing (hot flashes)
- feeling hot or cold
- chest pain
- dyspepsia (indigestion)
- skeletal pain (pain in joints or bones)

Tell your doctor about any symptoms that you develop while taking FROVA.

This is not a complete list of side effects. Talk to your doctor if you develop any symptoms that concern you.

How should I store FROVA?

Store FROVA at between 59°F to 86°F (15°C to 30°C). Protect FROVA from moisture. Discard after expiration date printed on package.

Keep FROVA and all medicines out of the reach of children.

General advice about the safe and effective use of FROVA.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use FROVA for a condition for which it was not prescribed. Do not give FROVA to other people, even if they have the same symptoms as you. People may be harmed if they take medicines that have not been prescribed for them.

This leaflet summarizes the most important information about FROVA. If you would like more information about FROVA, talk to your doctor. You can ask your doctor or pharmacist for information on FROVA that is written for healthcare professionals. You can also call 1-800-462-3636 or visit our website at www.FROVA.com.

What are the Ingredients in FROVA?

Active ingredient: frovatriptan succinate

Inactive ingredients: lactose NF, microcrystalline cellulose NF, colloidal silicon dioxide NF, sodium starch glycolate NF, magnesium stearate NF, hypromellose USP, polyethylene glycol 3000 USP, triacetin USP, and titanium dioxide USP

Manufactured for: Endo Pharmaceuticals Inc., Malvern, PA 19355

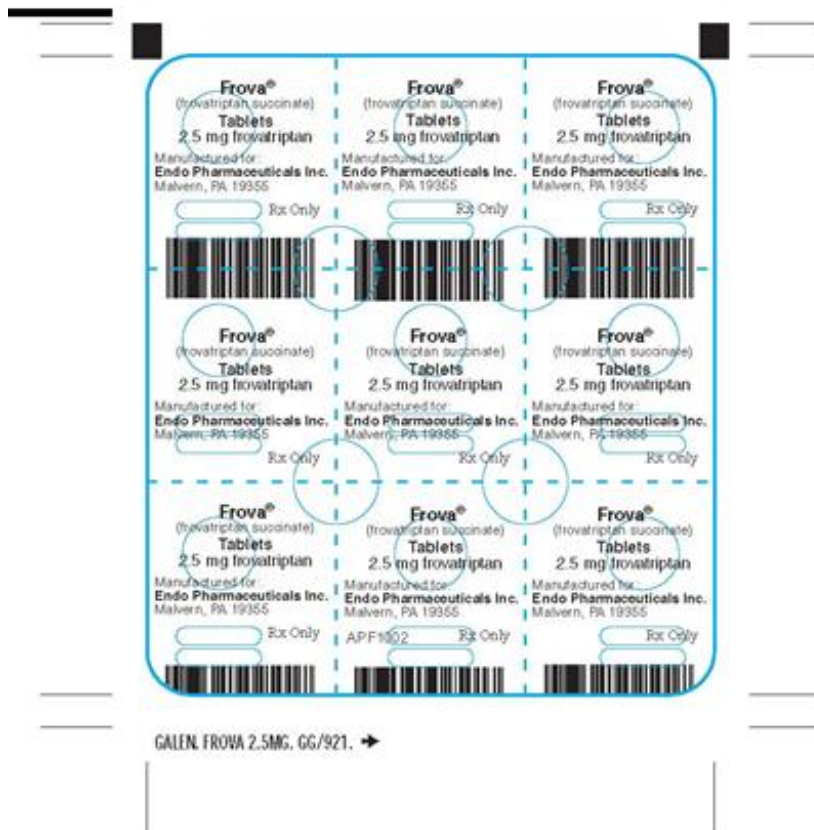
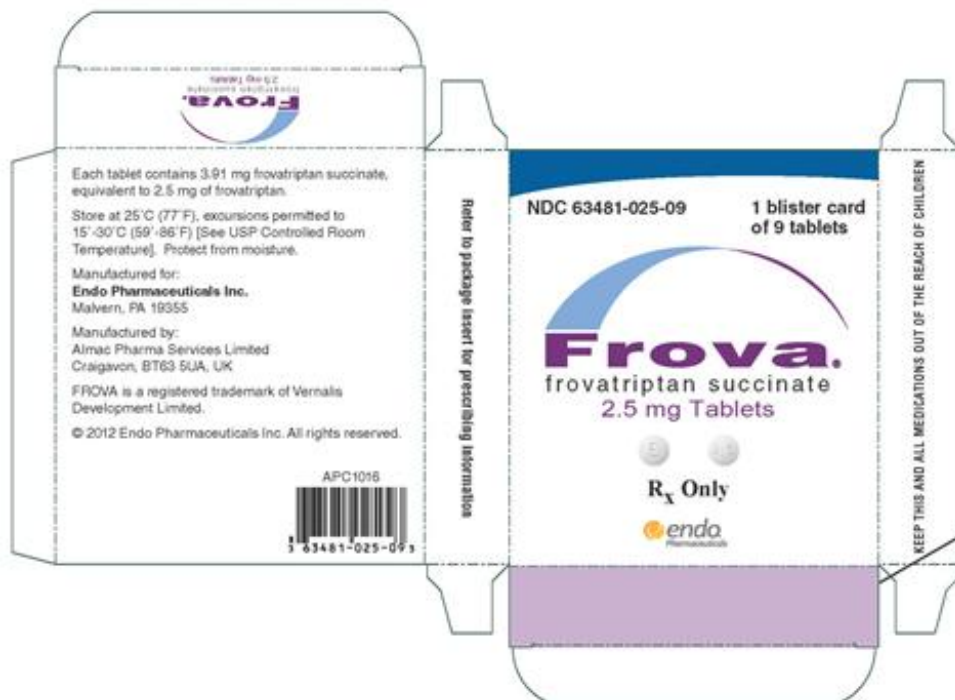
Manufactured by: Almac Pharma Services Limited, Craigavon, BT63 5UA, UK

FROVA is a registered trademark of Vernalis Development Limited.

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U.S. Patent Nos 5,962,501, 5,827,871, 5,637,611 and 5,464,864 and 5,616,603.

APX1009/1



FROVA

frovatriptan succinate tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:63481-025
Route of Administration	ORAL	DEA Schedule	

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
FROVATRIPTAN SUCCINATE (FROVATRIPTAN)	FROVATRIPTAN	2.5 mg

Inactive Ingredients	
Ingredient Name	Strength
LACTOSE	
CELLULOSE, MICROCRYSTALLINE	
SILICON DIOXIDE	
SODIUM STARCH GLYCOLATE TYPE A POTATO	
MAGNESIUM STEARATE	
HYPROMELLOSES	
POLYETHYLENE GLYCOL 3000	
TRIACETIN	
TITANIUM DIOXIDE	

Product Characteristics			
Color	WHITE	Score	no score
Shape	ROUND	Size	8mm
Flavor		Imprint Code	E;2;5
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63481-025-09	1 in 1 CARTON		
1		9 in 1 BLISTER PACK		
2	NDC:63481-025-12	6 in 1 CARTON		
2		2 in 1 BLISTER PACK		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021006	11/08/2001	

Labeler - Endo Pharmaceuticals Inc. (178074951)

